REMARKS/ARGUMENTS

After entry of this paper, claims 2, 3, 5, 6, 21, 23, 43-49, 51-58 and 60-66 are pending. Claims 1, 4, 7-20, 22, 24-42, 50 and 59 are canceled, without prejudice. Applicants reserve the right to prosecute any previously or currently canceled claims or subject matter in a divisional or continuation application filed during the pendency of the present application. Claims 2, 6, 21, 47-49, and 57-58 are amended to clarify the subject matter therein and remove all grounds for rejection, as discussed below. New claim 60 is a version of claim 59, rewritten for clarity. New claims 61-65 are supported in Example 3, Table 1 and throughout the specification as indicated below. New claim 66 is supported by the original claims and throughout the specification. More specifically, support for the amendments is found in the original specification on page 5, lines 3-10; page 13, lines 11-16; page 17, lines 28-30; page 23, lines 19-24; page 28, lines 3-4; page 45, lines 21-22; page 9, lines 9-14; page 13, lines 13-15; page 17, lines 13-30; page 22, lines 5-22; page 23, lines 19-24; and page 28, lines 3-4.

No new matter is added by these claim amendments and new claims which are presented to clarify the invention.

The Claimed Invention

Applicants are undisputedly the first to isolate and identify the Chfr polypeptide SEQ ID NO: 2 and a nucleotide sequence encoding it. Further Applicants are the first to identify that a cell in which a nucleotide sequence encoding Chfr is absent is sensitive to the activity of an agent that disrupts microtubule function, such as paclitaxeil. Consequently, Applicants are the first to identify and disclose that reagents, such as appropriate PCR primer sets, or kits containing appropriate PCR primer sets, that enable detection of the absence of a nucleotide sequence encoding Chfr in a tested cell (e.g., a biopsy of cancerous tissue or a tumor) are useful to determine whether a cancer may be successfully treated with such an agent, such as nocodozole or paclitaxel. As discussed below, nothing in the prior art provides any suggestion of Chfr, a nucleotide sequence encoding Chfr, or diagnostic reagents, kits or methods for detecting the absence of a

nucleotide sequence encoding Chfr and sensitivity to an agent that disrupts microtubule function.

Claim Objections

Claims 21, 23, and 43-48 are objected to for the phrase "identical to SEQ ID NO: 1".

Applicants respectfully request reconsideration of this objection for the following reason. Claim 21 has been amended to recite

> "A reagent useful for detecting expression of the chfr gene in a cell, said reagent consisting of a nucleic acid sequence of between 12 to 30 nucleic acids in length that specifically hybridizes to a nucleic acid fragment of the same length from SEQ ID NO: 1 or to the complete complement of said fragment."

This amendment is believed to clarify the claim by limiting it to a sequence that hybridizes *with specificity* to a 12-30 nucleic acid fragment of a similarly-sized fragment from SEQ ID NO: 1 or to that fragment's completely complementary sequence. The reagent is unambiguously defined by the knowledge of the sequence of SEQ ID NO: 1, the definition of the fragment as being within SEQ ID NO: 1, the defined size of the fragment, and the requirement that the reagent specifically hybridize to the selected fragment. This claim is supported by specification page 11, lines 12-26; page 17, line 14 to page 18, line 6 and Example 3, particularly Table 1.

Reconsideration and withdrawal of this objection is requested.

35 USC § 112, First Paragraph

1. *Claims 47-48 and 57-58 are rejected for allegedly unsupported use of "an anti-mitotic agent". The examiner suggests that the agent be described as stated in the specification at page 5, line 4; and page 27, lines 12-13 and 16-17, namely "an agent that disrupts microtubule function".*

In view of the amendment of claims 47 and 57 to revise the description of the agent, as suggested by the Examiner, Applicants respectfully request reconsideration and withdrawal of this rejection.

2. *Claims 2-3, 5-6, 21 and 23 are rejected for alleged lack of clear written description and new claims 43-59 are rejected allegedly for reasons of record in the Office Action dated June 4, 200, namely:*

   a. *Specifically, the examiner states that a complement to SEQ ID NO: 1 or fragment thereof allegedly encompasses partial or full length complements wherein a partial complement would be complementary by only a few nucleotides. Thus such a sequence has unknown structure.*

Applicants respectfully request reconsideration and withdrawal of this rejection in view of the amendments to claims 2, 21 and 49, requiring complete complementarity to the defined SEQ ID NO: 1 or defined small fragment thereof. These amendments are supported in the specification at page 11, line 15-20 and page 17, lines 15-17 and in the specification pages recited above. As indicated previously in the Office Action by the examiner with respect to the sequences of the prior art, once one of skill is provided with a nucleotide sequence, the provision of its complete complement is known in the art, without further teaching.

With regard to claim 6, this rejection is rendered moot by amendment.

   b. *Further the examiner states that a fragment of SEQ ID NO: 1 that is complementary and binds to chfr encompasses a fragment complementary to and binding to variants of SEQ ID NO: 1. Further the examiner states that the chfr gene must be identified as SEQ ID NO: 1 to avoid claiming variants.*

Applicants respectfully request reconsideration and withdrawal of this rejection. Applicants are fully entitled to claim variants of nucleotide sequences that encode SEQ ID NO: 2, the Chfr polypeptide by virtue of being the first to define the Chfr polypeptide sequence. Once such a sequence is defined, it is a simple matter to recite a variety of nucleotide sequences that encode SEQ ID NO: 2 or fragments of it. In view of the above-noted amendments, the definition of the fragments are precise in size. For example, as defined by the specification, any one of skill in the art with knowledge of the degeneracy of the genetic code may design a number of pairs of 12 to 30 nucleotide sequences that hybridize to the sense or antisense sequences of Chfr SEQ ID NO: 2. Examples of such

sequences are provided by the primer sequences used in the assay described in Example 3, Table 1 to detect Chfr expression in cancer cells. This claim language is supported thereby. Applicants are not required to reteach routine subject matter in their specification but are permitted to rely upon knowledge extant in the art at the time of filing. The knowledge of the different codons that express the amino acids of a protein are clearly known. Since Applicants are the first to identify the isolated protein, they are equally entitled to claim nucleotide sequences in addition to SEQ ID NO: 1 that may be readily presented to encode the same protein. Thus, Applicants request the examiner to reconsider this rejection in view of the above amendments.

c. *The examiner further asserts that a kit for detecting a mutation of chfr allegedly encompasses a reagent for detecting numerous variants of SEQ ID NO: 1. Additionally the examiner states that the two disclosed and detected mutations are an insufficient number of species of detected mutations.*

Applicants respectfully request reconsideration and withdrawal of this rejection in view of the elimination of the language "mutation of chfr" from all pending claims. However, please note that presence of a mutation may be indicated by lack of binding or weakened binding of one of the defined reagents of this invention. The two exemplary disclosed and detected mutations simply serve to demonstrate the utility of the compositions and methods of this invention.

However, to advance prosecution, Applicants have removed this language. Kit claims 49-58 are submitted to clearly define the structure of the reagents to one of skill in the art. No additional language is needed to describe such reagents to one of skill in the art. This ground for rejection may be withdrawn.

d.. *The language "an isolated sequence which is an antisense sequence of a sequence encoding at least AA 31-103, AA303-346, AA 476-641" is open language encompassing sequences with unknown structure of any length that contains a few antisense nucleotides of the encoding sequence.*

Applicants respectfully request reconsideration and withdrawal of this rejection as it has been rendered moot by amendment of the claims above.

e. *Further, the specification does not meet the written description requirement because it does not disclose sufficiently detailed "relevant identifying characteristics, functional characteristics with a known or disclosed correlation between function and structure or some combination thereof.*

Applicants respectfully request reconsideration and withdrawal of this rejection or further explanation of this ground of rejection. As amended, all of the claims are believed to be clearly described within the specification and their respective functions clearly explained. To address this rejection, Applicants request further explanation from the examiner or withdrawal of same.

In view of the above claim amendments and remarks, Applicants respectfully request reconsideration and withdrawal of all above grounds for rejection of the pending claims.

3. *Claims 2-3, 5-6, and 21 and claims 43-59 are rejected for allegedly only being enabled for the polynucleotide of SEQ ID NO: 1, not a complement or fragment thereof, a variant thereof, a method for detecting a mutation of chfr gene, and a sequence which is an antisense sequence of a sequence encoding a fragment of SEQ ID NO: 2. Specifically, the examiner reiterates the same rejections made in paragraph 2 above.*

Applicants respectfully request reconsideration and withdrawal of this rejection. As admitted by the examiner in reference to the sequences of the prior art, the provision of the sense sequence of a nucleic acid clearly provides one of skill in the art with the complement thereof. Such teaching is elementary. Applicants clearly contemplated the complementary and antisense sequences of the invention within the specification as originally filed. See, specification page 17, line 17 through page 18, line 6; page 24, line 21 through page 25, line 7; the assay and the sense and antisense primers of Table 1 of Example 3, page 37 et seq., among others. Using the primers in a method for detecting a mutation of *chfr* gene is also disclosed in Example 3. Further since the novel Chfr

polypeptide SEQ ID NO: 2 is defined, nucleotide sequences encoding it may be readily provided by one of skill in the art. SEQ ID NO: 1 is an example of such a sequence. One of skill in the art, as discussed above, may readily prepare a sequence which is antisense to any nucleotide sequence encoding SEQ ID NO: 2 or to a portion thereof, such as a number of the 3' or antisense primers of Table 1.

Applicants submit that based upon the pending claims and these remarks, this ground for rejection may be properly withdrawn.

4. *Claims 47-48 and 57-58 are rejected for allegedly being enabled for a kit useful for detecting sensitivity to killing of cancer cells by nocodazole or Taxol, wherein detection of lack of mRNA expression of SEQ ID NO: 1 is indicative of said sensitivity, but not enablement for detecting sensitivity of tumor cells to an anti-mitotic drug. The examiner admits at page 9, lines 15-17, that Example 4 demonstrates that cells that express chfr survive better when exposed to nocodazole or Taxol, whereas cells that do not express detectable chfr are more sensitive to such agent. The examiner argues that "only an absence of the mRNA of SEQ ID NO: 1 is indicative of increased susceptibility to cell killing by the drug nocodazole or taxol, as shown by Example 4"*

Applicants respectfully request reconsideration and withdrawal of this rejection. As amended, Applicants' claims are supported in the specification at page 26, line 27 through page 27, line 22 and in Example 4. Applicants' amended claims now reflect the concept of detecting a cell's sensitivity to killing by agents that disrupt microtubule function (including nocodazole and paclitaxel) by detecting the absence of expression of a nucleotide sequence that encodes Chfr SEQ ID NO: 2, such as SEQ ID NO: 1, with the reagents and kits of the present invention.

These amendments are believed to satisfy this rejection by the examiner.

5. *Claim 50 is rejected for allegedly being enabled only for a kit which analyzes the absence of the mRNA of SEQ ID NO: 1, not the substantial absence of a chfr gene, a mutation thereof or both.*

Cancellation of claim 50 renders this rejection moot.

35 USC § 112, Second Paragraph

Claims 47-48, and 57-58 are allegedly indefinite for use of "sensitivity". Claim 50 is allegedly indefinite for use of "substantial" absence. Claims 48 and 58 are allegedly indefinite for use of the trademark "TAXOL".

Applicants request reconsideration and withdrawal of these rejections. Applicants have amended the claims 47 and 57 to state that said sensitivity is sensitivity by killing by an agent that disrupts microtubule function, which appears to be acceptable to the examiner.

To advance prosecution thereof, Applicants have cancelled claim 50.

To advance prosecution thereof, Applicants have cancelled the word "TAXOL" from claims 48 and 58 and replaced it with the generic term "paclitaxel" in each case. Support for the interchangeability of these terms is provided by the attached copy of a copy (Labeled Exhibit A) of an entry in The American Heritage® Dictionary of the English Language, 4th Edit., Copyright 2000 by Houghton Mifflin Co., as it appears on the internet. This attachment provides evidence that those of skill in the art are well aware that the trademark TAXOL® is used to represent the generic compound, paclitaxel.

In view of these amendments, Applicants respectfully request reconsideration and withdrawal of this rejection.

35 USC § 102(b) Rejection

1. *Claims 2 and 59 are rejected under 35 USC § 102 (b) as allegedly anticipated by Boehringer Mannheim Biochemicals, 1994 Catalog, page 93 because claim 2 is drawn to a sequence complementary to SEQ ID NO: 1 and claim 59 is drawn to an antisense sequence of a sequence encoding three specific amino acid fragments. The examiner states that "Given the sequences taught by Boehringer, one could readily envision the claimed complement or antisense sequence, because a complement or antisense could be of any size, as long as it contains a few complementary or antisense nucleotides".*

Applicants respectfully request reconsideration and withdrawal of this rejection for the following reason. A rejection based on Section 102 must "anticipate" all aspects

of the claimed invention. Applicants' Chfr polypeptide SEQ ID NO: 2, as stated before, is a novel protein and thus the nucleotide sequence SEQ ID NO: 1 is novel and no prior art exists to challenge the novelty thereof. In view of the fact that Applicants have now specified in claim 2 that the complement of SEQ ID NO: 1 must be **complete or 100%**, none of the random 6-mer nucleotide primers of the cited document anticipates or even suggests the specific SEQ ID NO: 1 (i.e., 2672 nucleotides with a coding sequence of 1992 nucleotides) or its complete complement. This rejection must be withdrawn, as the document itself does not teach the invention of the claim 2.

Cancellation of claim 59 renders this rejection moot as to that claim.

The mere existence of 6-mer random primers cannot anticipate completely novel and specific sequences of more than 1992 nucleotides as recited by claim 2. Absent knowledge of the complete isolated Chfr polypeptide SEQ ID NO: 2 itself or at least one isolated nucleotide sequence capable of encoding same, such as SEQ ID NO: 1, one of skill in the art armed with the 6-mers of Boehringer would have **no** ability to use such sequences to create any nucleotide sequence encoding SEQ ID NO: 2.

Reconsideration and withdrawal of this rejection is requested.

2. *Claims 21,and 44-48 are rejected as allegedly anticipated by at least one of the following documents:*

   (a) *JP 06303997, 1994 GenBank Accession No: AAQ75652 (claims 21, 47-48, which refers to a 21-nucleotide sequence which is identical to 21 nucleotides (nt 2658 to 2678) of Applicants' SEQ ID NO: 1.*

   (b) *US Patent No. 5,610,054, GenBank Accession No: I57653 (claims 21,44), which refers to a 15-nucleotide sequence which contains 13 nucleotides that are identical to 13 nucleotides (nt 129-141) of Applicants' SEQ ID NO: 1.*

   (c) *Gold, D. P. et al, 1993 GenBank Accession No: S86452 (Claims 21, 45), which refers to a 30-nucleotide sequence which contains 14 nucleotides that are identical to 14 nucleotides (nt 98-111) of Applicants' SEQ ID NO: 1.*

   (d) *George, JF et al, 1992, GenBank Accession No: S81367 (Claims 21, 46), which refers to a 27-nucleotide sequence which contains 14 nucleotides*

that are identical to 14 nucleotides (nt 138-151) of Applicants' SEQ ID NO: 1.

In all cases, the examiner states that one of skill in the art could readily envision the claimed complementary sequence from the sequence provided by the document.

Applicants respectfully request reconsideration and withdrawal of this rejection for the following reasons.

Documents (a) through (d) refer to nucleotide sequences directed to other targets that are not nucleotide sequences encoding Chfr and do not anticipate all of the requirements of amended claims 21 and 44-48.

For example, Document (a) is a poly-A sequence, not a ***coding*** sequence. The amendment to Claim 21 that requires the nucleotide sequence to be a fragment of the **coding** sequence of SEQ ID NO: 1 removes any applicability of the primer of Document (a) as a Section 102 reference against claim 21 or any of dependent claims 44-48.

Further, the amendment to Claim 21 that requires the nucleic acid sequences to specifically hybridize to a fragment ***of the same length*** in SEQ ID NO: 1 or in its complete complement removes the applicability of Documents (b)-(d) from these claims. Each primer (b) through (d) refers to a sequence of which only **a portion** specifically hybridizes to fragments of the antisense sequence of Applicants' SEQ ID NO: 1. For example, primer (b) is a sequence containing 15 nucleotides, only 13 of which are identical to a fragment of 15 nucleotides of the complement of Applicants' SEQ ID NO: 1. As another example, the primer of (c) is 30 nucleotides in length, and only 14 of these nucleotides are specifically hybridizable to 30 nucleotides of the complement of Applicants' SEQ ID NO: 1. As the third example, primer (d) is 27 nucleotides in length. Only 14 of those nucleotides are specifically hybridizable to 27 nucleotides of the complement of Applicants' SEQ ID NO: 1.

Because these primers of the prior art do not meet all requirements of amended claim 21 (and consequently its dependent claims), this basis for rejection may be properly withdrawn in view of these amendments.

Further, this ground for rejection cannot be asserted against new claim 60, which requires a primer set, one primer being a fragment that specifically hybridizes to a 12-50 nucleic acid fragment that encodes Chfr SEQ ID NO: 2 and the other primer being a fragment that specifically hybridizes to a 12-50 nucleic acid fragment of the complete complement of a nucleotide sequence encoding Chfr. Because the isolated Chfr protein was not known before its disclosure in this application, none of this art can teach or suggest selection of appropriate primer pairs for the detection and amplification of Chfr. Thus, claim 61 and its dependent claims are free of this art.

35 USC § 103(a) Rejections

1. *Claim 3 is rejected under 35 USC § 103(a) as allegedly being anticipated by the above-cited Boehringer document in view of Sambrook et al. (1989, Molecular Cloning, A Laboratory Manuel, 2nd Ed., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, p. 10.6-10.7).*

   The Examiner asserted that it would have been obvious to one of skill in the art to make the 6-mer primers of Boehringer synthetically or recombinantly as motivated by Sambrook with a reasonable expectation of success.

Applicants respectfully request reconsideration and withdrawal of this rejection for the following reason.

As discussed above, nothing in these documents suggests that one of skill in the art use the 6-mer random primers of Boehringer to create a novel nucleotide sequence, such as SEQ ID NO: 1 or its complete complement, that encodes the novel protein Chfr SEQ ID NO: 2. Thus Boehringer does not teach or suggest how to express such sequences in any way. The teachings of Sambrook are only general teachings regarding detecting the presence of nucleic acid sequences. Sambrook adds nothing to Boehringer to teach or suggest SEQ ID NO: 1 or its complete complement.

No combination of Boehringer or Sambrook teaches or suggests the sequences, reagents, or kits of Applicants' invention which teach detecting the absence of expression of any nucleotide sequence encoding Chfr SEQ ID NO: 2 and correlate the same with the sensitivity of a subject's cells to agents that disrupt microtubules, such as paclitaxel.

This rejection may be properly withdrawn.

2. *Claims 23, 43, and 49-58 are rejected as being obvious over JP 06303997, previously cited in view of US Patent No. 5,324,630. As discussed above, JP 063030997 refers to the analysis of cDNA and gene expression by amplification and refers to a single 15-mer primer which is 100% identical to a non-coding sequence found in SEQ ID NO: 1. US 5,324,630 refers to a diagnostic kit for Lyme Disease using a single labeled nucleic acid probe. The examiner finds its prima facie obvious to use the '997 primer, labeled as taught by '630 for use in the diagnosis of gene expression as taught by '997 in a kit.*

Applicants respectfully request reconsideration and withdrawal of this rejection for the following reason.

The primer of JP 06303997, which is directed to a polyA sequence, even if used in a method employing a single nucleic probe for a disease, as taught by '630 does not suggest the reagent of claims 23 and 43, nor the kit of amended claims 49-58. Such a poly-A sequence would not be *specifically* hybridizable to a nucleotide sequence of the same length from SEQ ID NO:1, as required by independent amended claim 21. This primer clearly hybridizes to other targets. Thus, even if used as a single labeled nucleic acid probe as taught in '630 for Lyme Disease, this prior art combination fails to suggest the invention of claims 23 and 43.

Further this combination of the primer of JP 06303997 with the method of '630 does not suggest to one of skill in the art *a set* of primers as specifically defined by new claim 61, nor methods nor kits requiring two specifically hybridizing sequences to SEQ ID NO: 1 or its complement. Nor does this combination suggest anything at all about employing such primer sets for the identification or amplification of a nucleotide sequence encoding Chfr protein in a cell for any reason. This is true despite the fact that diagnostic kits for detection of other genes involved in other diseases, e.g., Lyme Disease, were known.

There is no suggestion in this combination of any of the pending claims. One of skill in the art would have *not* have been led by either document alone or in combination to produce the compositions now claimed by the pending claims. Hindsight cannot properly be employed in constructing an obviousness rejection.

This rejection should be withdrawn as against all pending claims.

All rejections having been eliminated by either the above arguments or amendment of the claims, Applicants respectfully request that the examiner allow all pending claims to proceed to allowance in due course.

The Director is hereby authorized to charge any deficiency in any fees due with the filing of this paper or credit any overpayment in any fees to our Deposit Account Number 08-3040.

Respectfully submitted,

HOWSON AND HOWSON
Attorneys for Applicants

By Mary E. Bak

Mary E. Bak,
Registration No. 31,215
Spring House Corporate Center
Box 457
Spring House, PA 19477
Telephone: (215) 540-9200
Telefacsimile: (215) 540-5818

Application No. 10/048,046 Exhibit A

CONTENTS · INDEX · ILLUSTRATIONS · BIBLIOGRAPHIC RECORD

The American Heritage® Dictionary of the English Language: Fourth Edition. 2000.

Taxol

SYLLABICATION: Tax·ol

PRONUNCIATION: tăk'sôl'

A trademark used for the drug paclitaxel.

CONTENTS · INDEX · ILLUSTRATIONS · BIBLIOGRAPHIC RECORD

< taxo– taxon >